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SEQUENCE LISTING

<110> OUIMET et al.

<120> Novel membrane-bound metalloprotease NEP II and the use thereof for screening inhibitors useful in therapy

<130> P06910US0/BAS

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<150> PCT/FR99/00807

<151> 1999-04-07

<150> FR/9804389

<151> 1998-04-08

<160> 29

<170> PatentIn Ver. 2.1

<210> 1

<211> 2765

<212> DNA

<213> Rattus rattus

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<221> CDS

<222> (107) ... (2428)

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Arg Arg Leu Gly Phe Val Glu Cys Gly Leu Leu Val Leu Leu Thr Leu
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Leu Leu Met Gly Ala Ile Val Thr Leu Gly Val Phe Tyr Ser Ile Gly
40 45 50

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Lys Gln Leu Pro Leu Leu Asn Ser Leu Leu His Val Ser Arg His Glu
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aac atg gac cag tca aag aaa ccc tgc gac aac ttc tat cag tat gct Asn Met Asp Gln Ser Lys Lys Pro Cys Asp Asn Phe Tyr Gln Tyr Ala	100	105	110	115	
tgc gga ggc tgg cta cgg cac cat gtg atc ccc gag acc aac tcc aga Cys Gly Gly Trp Leu Arg His His Val Ile Pro Glu Thr Asn Ser Arg	120	125	130	451	
tac agc gtc ttt gac atc ctt cgg gat gag ctg gag gtc atc ctc aaa Tyr Ser Val Phe Asp Ile Leu Arg Asp Glu Leu Glu Val Ile Leu Lys	135	140	145	499	
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gcc aag aca ctg tac cgc tcc tgc atg aac cag agt gtg ata gag aag Ala Lys Thr Leu Tyr Arg Ser Cys Met Asn Gln Ser Val Ile Glu Lys	165	170	175	595	
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Ser Arg His Val Ile Tyr Ile Asp Gln Pro Thr Leu Gly Met Pro Ser
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Arg Glu Tyr Tyr Phe Lys Glu Asp Ser His Arg Val Arg Glu Ala Tyr
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Leu Gln Phe Met Thr Ser Val Ala Thr Met Leu Arg Arg Asp Leu Asn
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Leu Pro Gly Glu Thr Asp Leu Val Gln Glu Glu Met Ala Gln Val Leu
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His Leu Glu Thr His Leu Ala Asn Ala Thr Val Pro Gln Glu Lys Arg
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His Asp Val Thr Ala Leu Tyr His Arg Met Gly Leu Glu Glu Leu Gln
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Val Leu Ser Ser Val Gln Val Glu Leu Leu Pro Asn Glu Glu Val Val
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Val Tyr Gly Ile Pro Tyr Leu Glu Asn Leu Glu Glu Ile Ile Asp Val
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Phe Pro Ala Gln Thr Leu Gln Asn Tyr Leu Val Trp Arg Leu Val Leu
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Tyr Arg Lys Ala Leu Tyr Gly Thr Thr Met Glu Glu Val Arg Trp Arg
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Glu Leu Ile Glu Lys Ile Arg Ser Val Phe Val Asp Asn Leu Asp Glu

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485 490 495
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Asp Leu Tyr Phe Glu Asn Gly Leu Gln Asn Leu Lys Asn Asn Ala Gln
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Arg Ser Leu Lys Lys Leu Arg Glu Lys Val Asp Gln Asn Leu Trp Ile
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Gln Pro Gln Ala Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His
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Glu Ile Thr His Gly Phe Asp Asp Asn Gly Arg Asn Phe Asp Lys Asn
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Gly Asn Met Leu Asp Trp Trp Ser Asn Phe Ser Ala Arg His Phe Arg
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Gln Gln Ser Gln Cys Met Ile Tyr Gln Tyr Ser Asn Phe Ser Trp Glu
645 650 655
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660 665 670
Ile Ala Asp Asn Gly Gly Val Arg Gln Ala Tyr Lys Ala Tyr Leu Gln
675 680 685
Trp Leu Ala Glu Gly Gly Arg Asp Gln Arg Leu Pro Gly Leu Asn Leu
690 695 700
Thr Tyr Ala Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp Cys Gly
705 710 715 720
Ser Tyr Arg Pro Glu Phe Ala Ile Gln Ser Ile Lys Thr Asp Val His
725 730 735
Ser Pro Leu Lys Tyr Arg Val Leu Gly Ser Leu Gln Asn Leu Pro Gly
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aacacccttg gggaaaacat tgctgacaac ggaggggtgc ggcaagccta taaggcctac 240
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Phe Arg Glu Gln Ser Glu Cys Met Ile Tyr Gln Tyr Gly Asn Tyr Ser
35 40 45
Trp Asp Leu Ala Asp Glu Gln Asn Val Asn Gly Phe Asn Thr Leu Gly
50 55 60
Glu Asn Ile Ala Asp Asn Gly Gly Val Arg Gln Ala Tyr Lys Ala Tyr
65 70 75 80
Leu Lys Trp Met Ala Glu Gly Gly Lys Asp Gln Gln Leu Pro Gly Leu
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SEQUENCE LISTING

<110> OUIMET et al.

<120> Novel membrane-bound metalloprotease NEP II and the use thereof for screening inhibitors useful in therapy

<130> P06910US0/BAS

<140>

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<150> PCT/FR99/00807

<151> 1999-04-07

<150> FR/9804389

<151> 1998-04-08

<160> 29

<170> PatentIn Ver. 2.1

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<212> DNA

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Lys Gln Leu Pro Leu Leu Asn Ser Leu Leu His Val Ser Arg His Glu
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CTG GAG CGG CAG TTG GCT GTG TTG AAC TCG CAG TTC AAC AGG CGC GTC Leu Glu Arg Gln Leu Ala Val Leu Asn Ser Gln Phe Asn Arg Arg Val 215 220 225	787
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GTC ATC TAC ATA GAC CAG CCC ACC TTG GGC ATG CCC TCC CGG GAG TAC Val Ile Tyr Ile Asp Gln Pro Thr Leu Gly Met Pro Ser Arg Glu Tyr 245 250 255	883
TAT TTC AAG GAA GAC AGC CAC CGG GTA CGG GAA GCC TAC CTG CAG TTC Tyr Phe Lys Glu Asp Ser His Arg Val Arg Glu Ala Tyr Leu Gln Phe 260 265 270 275	931
ATG ACA TCA GTG GCC ACT ATG CTG AGG AGA GAC CTG AAC CTG CCC GGG Met Thr Ser Val Ala Thr Met Leu Arg Arg Asp Leu Asn Leu Pro Gly 280 285 290	979
GAG ACC GAT TTG GTG CAG GAG GAA ATG GCA CAG GTG CTG CAT CTG GAG Glu Thr Asp Leu Val Gln Glu Glu Met Ala Gln Val Leu His Leu Glu 295 300 305	1027
ACA CAT CTG GCC AAC GCC ACG GTC CCC CAG GAG AAA AGG CAT GAT GTC	1075

Thr His Leu Ala Asn Ala Thr Val Pro Gln Glu Lys Arg His Asp Val			
310	315	320	
ACC GCC CTG TAT CAC CGA ATG GGC CTG GAG GAG CTG CAG GAA AGG TTT			1123
Thr Ala Leu Tyr His Arg Met Gly Leu Glu Glu Leu Gln Glu Arg Phe			
325	330	335	
GGT CTG AAG GGG TTT AAC TGG ACT CTC TTC ATA CAA AAC GTG CTG TCT			1171
Gly Leu Lys Gly Phe Asn Trp Thr Leu Phe Ile Gln Asn Val Leu Ser			
340	345	350	355
TCT GTG CAA GTT GAG CTG CTC CCG AAT GAG GAG GTG GTG GTC TAT GGC			1219
Ser Val Gln Val Glu Leu Leu Pro Asn Glu Glu Val Val Val Tyr Gly			
360	365	370	
ATC CCC TAC CTG GAG AAT CTT GAG GAG ATC ATT GAC GTC TTC CCA GCA			1267
Ile Pro Tyr Leu Glu Asn Leu Glu Glu Ile Ile Asp Val Phe Pro Ala			
375	380	385	
CAG ACC TTG CAA AAC TAC CTG GTG TGG CGC CTG GTG CTA GAT CGC ATC			1315
Gln Thr Leu Gln Asn Tyr Leu Val Trp Arg Leu Val Leu Asp Arg Ile			
390	395	400	
GGC AGC CTG AGC CAG AGA TTC AAA GAA GCG CGT GTG GAC TAC CGC AAG			1363
Gly Ser Leu Ser Gln Arg Phe Lys Glu Ala Arg Val Asp Tyr Arg Lys			
405	410	415	
GCG CTG TAC GGT ACA ACC ATG GAG GAA GTA CGC TGG CGG GAG TGT GTC			1411
Ala Leu Tyr Gly Thr Thr Met Glu Glu Val Arg Trp Arg Glu Cys Val			
420	425	430	435
AGC TAT GTC AAC AGC AAC ATG GAG AGT GCC GTG GGC TCC CTC TAC ATC			1459
Ser Tyr Val Asn Ser Asn Met Glu Ser Ala Val Gly Ser Leu Tyr Ile			
440	445	450	
AAG CGG GCC TTC TCC AAG GAC AGC AAG AGC ATA GTC AGT GAG CTT ATC			1507
Lys Arg Ala Phe Ser Lys Asp Ser Lys Ser Ile Val Ser Glu Leu Ile			
455	460	465	
GAG AAG ATA CGG TCC GTG TTT GTG GAT AAC CTG GAC GAG TTG AAC TGG			1555
Glu Lys Ile Arg Ser Val Phe Val Asp Asn Leu Asp Glu Leu Asn Trp			
470	475	480	
ATG GAT GAG GAA TCC AAG AAA AAG GCC CAG GAA AAG GGC TTG AAT ATC			1603
Met Asp Glu Glu Ser Lys Lys Ala Gln Glu Lys Ala Leu Asn Ile			
485	490	495	
CGG GAA CAG ATC GGC TAC CCT GAC TAC ATT TTG GAA GAC AAT AAC AGA			1651
Arg Glu Gln Ile Gly Tyr Pro Asp Tyr Ile Leu Glu Asp Asn Asn Arg			
500	505	510	515
CAC CTG GAT GAG GAA TAC TCC AGT CTG ACT TTC TCA GAG GAC CTG TAT			1699
His Leu Asp Glu Glu Tyr Ser Ser Leu Thr Phe Ser Glu Asp Leu Tyr			
520	525	530	
TTT GAG AAC GGG CTT CAG AAC CTC AAG AAC AAT GCC CAA AGG AGC CTC			1747
Phe Glu Asn Gly Leu Gln Asn Leu Lys Asn Asn Ala Gln Arg Ser Leu			

535	540	545	
AAG AAA CTT CGG GAA AAG GTG GAC CAG AAT CTC TGG ATC ATT GGG GCT Lys Lys Leu Arg Glu Lys Val Asp Gln Asn Leu Trp Ile Ile Gly Ala 550	555	560	1795
GCA GTG GTC AAT GCA TTC TAC TCC CCA AAC AGA AAC CTG ATC GTC TTT Ala Val Val Asn Ala Phe Tyr Ser Pro Asn Arg Asn Leu Ile Val Phe 565	570	575	1843
CCA GCG GGG ATC CTC CAG CCA CCC TTC AGC AAG GAC CAA CCA CAG Pro Ala Gly Ile Leu Gln Pro Pro Phe Phe Ser Lys Asp Gln Pro Gln 580	585	590	1891
GCC TTG AAT TTC GGG GGC ATC GGG ATG GTG ATT GGA CAC GAG ATC ACA Ala Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His Glu Ile Thr 600	605	610	1939
CAC GGC TTT GAT GAT AAC GGT CGG AAC TTT GAC AAG AAT GGC AAC ATG His Gly Phe Asp Asp Asn Gly Arg Asn Phe Asp Lys Asn Gly Asn Met 615	620	625	1987
CTG GAC TGG TGG AGC AAC TTC TCG GCC CGG CAC TTC CGA CAG CAG TCA Leu Asp Trp Trp Ser Asn Phe Ser Ala Arg His Phe Arg Gln Gln Ser 630	635	640	2035
CAG TGT ATG ATT TAT CAG TAC AGC AAC TTC TCT TGG GAA CTA GCA GAC Gln Cys Met Ile Tyr Gln Tyr Ser Asn Phe Ser Trp Glu Leu Ala Asp 645	650	655	2083
AAC CAG AAT GTG AAC GGA TTC AGC ACC CTC GGG GAG AAC ATC GCC GAC Asn Gln Asn Val Asn Gly Phe Ser Thr Leu Gly Glu Asn Ile Ala Asp 660	665	670	2131
AAC GGC GGT GTG CGG CAG GCA TAC AAG GCT TAC CTA CAG TGG CTA GCT Asn Gly Val Arg Gln Ala Tyr Lys Ala Tyr Leu Gln Trp Leu Ala 680	685	690	2179
GAA GGC GGC AGA GAC CAG AGA CTG CCG GGA CTG AAC CTG ACC TAT GCT Glu Gly Gly Arg Asp Gln Arg Leu Pro Gly Leu Asn Leu Thr Tyr Ala 695	700	705	2227
CAG CTT TTC TTC ATT AAC TAT GCC CAG GTG TGG TGT GGG TCC TAC AGG Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp Cys Gly Ser Tyr Arg 710	715	720	2275
CCG GAG TTC GCC ATC CAG TCC ATC AAG ACA GAT GTC CAC AGT CCT CTT Pro Glu Phe Ala Ile Gln Ser Ile Lys Thr Asp Val His Ser Pro Leu 725	730	735	2323
AAG TAC AGG GTG CTG GGC TCA CTA CAG AAC CTA CCA GGC TTC TCT GAG Lys Tyr Arg Val Leu Gly Ser Leu Gln Asn Leu Pro Gly Phe Ser Glu 740	745	750	2371
CGC TTC CAC TGC CCA CGA GGC AGC CCC ATG CAC CCT ATG AAT CGA TGT Ala Phe His Cys Pro Arg Gly Ser Pro Met His Pro Met Asn Arg Cys 760	765	770	2419

CGC ATC TGG TAGCCAAGGC TGAGCTATGC TGCGGCCCAC GCCCCGCCAC 2468
Arg Ile Trp

CCAGAGGCTT CGTGAATGGT GTAGCCGGCA TAGATGTGCA GGTTGTTGCC TGAAGGCCAC 2528
TGGAGGCCACC AGCCAGCCCT CCGCGCCAG CCTAGAGGGC AGCCACCCGC CCACATCTGG 2588
GATGAGTGGT GGTGCCTGGT CCTGCGCCTT TTCCGGCCAG TGAGGGTCAG CGGCCCGGTA 2648
GGAGCAGTCA GCTGTCCCCC ACCCTTTCA TAGTGTGTGG CTAAATGTCC TCGAGCTTCA 2708
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Cys Gly Arg Arg Arg Leu Gly Phe Val Glu Cys Gly Leu Leu Val Leu
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Leu Thr Leu Leu Leu Met Gly Ala Ile Val Thr Leu Gly Val Phe Tyr
35 40 45

Ser Ile Gly Lys Gln Leu Pro Leu Leu Asn Ser Leu Leu His Val Ser
50 55 60

Arg His Glu Arg Thr Val Val Lys Arg Val Leu Arg Asp Ser Ser Gln
65 70 75 80

Lys Ser Asp Ile Cys Thr Thr Pro Ser Cys Val Ile Ala Ala Ala Arg
85 90 95

Ile Leu Gln Asn Met Asp Gln Ser Lys Lys Pro Cys Asp Asn Phe Tyr
100 105 110

Gln Tyr Ala Cys Gly Gly Trp Leu Arg His His Val Ile Pro Glu Thr
115 120 125

Asn Ser Arg Tyr Ser Val Phe Asp Ile Leu Arg Asp Glu Leu Glu Val
130 135 140

Ile Leu Lys Gly Val Leu Glu Asp Ser Ser Val Gln His Arg Pro Ala
145 150 155 160

Val Glu Lys Ala Lys Thr Leu Tyr Arg Ser Cys Met Asn Gln Ser Val
165 170 175

Ile Glu Lys Arg Asp Ser Glu Pro Leu Leu Asn Val Leu Asp Met Ile

180

185

190

Gly Gly Trp Pro Val Ala Met Asp Lys Trp Asn Glu Thr Met Gly Pro
195 200 205

Lys Trp Glu Leu Glu Arg Gln Leu Ala Val Leu Asn Ser Gln Phe Asn
210 215 220

Arg Arg Val Leu Ile Asp Leu Phe Ile Trp Asn Asp Asp Gln Asn Ser
225 230 235 240

Ser Arg His Val Ile Tyr Ile Asp Gln Pro Thr Leu Gly Met Pro Ser
245 250 255

Arg Glu Tyr Tyr Phe Lys Glu Asp Ser His Arg Val Arg Glu Ala Tyr
260 265 270

Leu Gln Phe Met Thr Ser Val Ala Thr Met Leu Arg Arg Asp Leu Asn
275 280 285

Leu Pro Gly Glu Thr Asp Leu Val Gln Glu Glu Met Ala Gln Val Leu
290 295 300

His Leu Glu Thr His Leu Ala Asn Ala Thr Val Pro Gln Glu Lys Arg
305 310 315 320

His Asp Val Thr Ala Leu Tyr His Arg Met Gly Leu Glu Glu Leu Gln
325 330 335

Glu Arg Phe Gly Leu Lys Gly Phe Asn Trp Thr Leu Phe Ile Gln Asn
340 345 350

Val Leu Ser Ser Val Gln Val Glu Leu Leu Pro Asn Glu Glu Val Val
355 360 365

Val Tyr Gly Ile Pro Tyr Leu Glu Asn Leu Glu Glu Ile Ile Asp Val
370 375 380

Phe Pro Ala Gln Thr Leu Gln Asn Tyr Leu Val Trp Arg Leu Val Leu
385 390 395 400

Asp Arg Ile Gly Ser Leu Ser Gln Arg Phe Lys Glu Ala Arg Val Asp
405 410 415

Tyr Arg Lys Ala Leu Tyr Gly Thr Thr Met Glu Glu Val Arg Trp Arg
420 425 430

Glu Cys Val Ser Tyr Val Asn Ser Asn Met Glu Ser Ala Val Gly Ser
435 440 445

Leu Tyr Ile Lys Arg Ala Phe Ser Lys Asp Ser Lys Ser Ile Val Ser
450 455 460

Glu Leu Ile Glu Lys Ile Arg Ser Val Phe Val Asp Asn Leu Asp Glu
465 470 475 480

Leu Asn Trp Met Asp Glu Glu Ser Lys Lys Ala Gln Glu Lys Ala

485

490

495

Leu Asn Ile Arg Glu Gln Ile Gly Tyr Pro Asp Tyr Ile Leu Glu Asp
 500 505 510

Asn Asn Arg His Leu Asp Glu Glu Tyr Ser Ser Leu Thr Phe Ser Glu
 515 520 525

Asp Leu Tyr Phe Glu Asn Gly Leu Gln Asn Leu Lys Asn Asn Ala Gln
 530 535 540

Arg Ser Leu Lys Lys Leu Arg Glu Lys Val Asp Gln Asn Leu Trp Ile
 545 550 555 560

Ile Gly Ala Ala Val Val Asn Ala Phe Tyr Ser Pro Asn Arg Asn Leu
 565 570 575

Ile Val Phe Pro Ala Gly Ile Leu Gln Pro Pro Phe Phe Ser Lys Asp
 580 585 590

Gln Pro Gln Ala Leu Asn Phe Gly Gly Ile Gly Met Val Ile Gly His
 595 600 605

Glu Ile Thr His Gly Phe Asp Asp Asn Gly Arg Asn Phe Asp Lys Asn
 610 615 620

Gly Asn Met Leu Asp Trp Trp Ser Asn Phe Ser Ala Arg His Phe Arg
 625 630 635 640

Gln Gln Ser Gln Cys Met Ile Tyr Gln Tyr Ser Asn Phe Ser Trp Glu
 645 650 655

Leu Ala Asp Asn Gln Asn Val Asn Gly Phe Ser Thr Leu Gly Glu Asn
 660 665 670

Ile Ala Asp Asn Gly Gly Val Arg Gln Ala Tyr Lys Ala Tyr Leu Gln
 675 680 685

Trp Leu Ala Glu Gly Gly Arg Asp Gln Arg Leu Pro Gly Leu Asn Leu
 690 695 700

Thr Tyr Ala Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp Cys Gly
 705 710 715 720

Ser Tyr Arg Pro Glu Phe Ala Ile Gln Ser Ile Lys Thr Asp Val His
 725 730 735

Ser Pro Leu Lys Tyr Arg Val Leu Gly Ser Leu Gln Asn Leu Pro Gly
 740 745 750

Phe Ser Glu Ala Phe His Cys Pro Arg Gly Ser Pro Met His Pro Met
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Asn Arg Cys Arg Ile Trp
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ATCTACCACT ACAGGCAACTA CTCCCTGGGAC CTGGCAGACG AACAGAACGT GAACGGATT 180
AACACCCCTTG GGGAAAACAT TGCTGACAAAC GGAGGGGTGC GGCAAGCCTA TAAGGCCTAC 240
CTCAAGTGGA TGGCAGAGGG TGGCAAGGAC CAGCAGCTGC CGGGCCTGGA TCTCACCCAT 300
GAGCAGCTCT TCTTCATCAA CTATGCC 327

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Lys Asn Gly Asn Met Met Asp Trp Trp Ser Asn Phe Ser Thr Gln His
20 25 30
Phe Arg Glu Gln Ser Glu Cys Met Ile Tyr Gln Tyr Gly Asn Tyr Ser
35 40 45
Trp Asp Leu Ala Asp Glu Gln Asn Val Asn Gly Phe Asn Thr Leu Gly
50 55 60
Glu Asn Ile Ala Asp Asn Gly Gly Val Arg Gln Ala Tyr Lys Ala Tyr
65 70 75 80
Leu Lys Trp Met Ala Glu Gly Gly Lys Asp Gln Gln Leu Pro Gly Leu
85 90 95
Asp Leu Thr His Glu Gln Leu Phe Phe Ile Asn Tyr Ala Gln Val Trp
100 105 110
Cys Gly Cys Lys
115

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8